Typical and atypical antipsychotics increase risk of sudden cardiac death

QUESTION

Question: What is the risk of sudden cardiac death with typical and atypical antipsychotics?

People: 279 907 Medicaid enrollees, aged 34–74 years (mean 45.7 years; 65.2% women), who were either currently taking a single antipsychotic ($n = 93\,307$) or no antipsychotics ($n = 186\,600$). Eligible antipsychotic users were those having at least one qualifying day of use of antipsychotic drugs during the study period. Two controls were randomly selected for each antipsychotic user, with matching for age, gender and first day of follow-up (defined as the first qualifying day for each antipsychotic user). Controls could subsequently become users of antipsychotic drugs. As well as the overall cohort, a subcohort matched for propensity scores was used in secondary analyses. Follow-up ended at the end of the study period, death, termination of Medicaid enrolment or if the participant subsequently met any of the study exclusion criteria. People could re-enter the study if they left it. Exclusion criteria: registration with Medicaid for <2 years; not eligible for full pharmacy benefits; not a regular user of medical care (<1 filled prescription and <1 outpatient visit in each of the preceding 2 years); high risk of death from non-cardiac causes. Follow-up did not include time spent in hospital or the 30 days after discharge.

Setting: Tennessee, USA; 1 January 1990 to 31 December 2005.

Risk factors: Atypical or typical antipsychotic use. Current use of antipsychotic was defined as the days between filling the prescription until the prescribed medication would have run out, when the person was most likely to be taking the drugs. Indeterminate use was the period up to 90 days after finishing the current drug. Former use was defined as any time after the first antipsychotic use that was not classified as current or indeterminate use. Non-use was defined as any days without antipsychotic prescription and with no antipsychotic use in the past. Antipsychotic use was categorised by approximate chlorpromazine dose equivalents, with <100 mg chlorpromazine defined as low dose, 100–299 mg as moderate dose and ≥ 300 mg as high dose. Typical antipsychotics assessed were thioridazine and haloperidol, and atypicals were clozapine, quetiapine, olanzapine and risperidone. Results were adjusted for demographic characteristics and comorbid conditions at

baseline. Summary cardiovascular risk scores were calculated from baseline cardiovascular and somatic variables (score range 0–19, higher score indicating greater risk).

Outcomes: Sudden cardiac death occurring in the community, identified using death certificates.

METHODS

Design: Retrospective cohort study.

Follow-up period: 16 years.

MAIN RESULTS

There were 1870 sudden cardiac deaths during the study period, equivalent to 17.9 per 10 000 person years. Current users of typical and atypical antipsychotics were significantly more likely to have sudden cardiac death than antipsychotic non-users (typical antipsychotics: incidence rate ratio (IRR) 1.99, 95% confidence interval (CI) 1.68 to 2.34; atypical antipsychotics: IRR 2.26, 95% CI 1.88 to 2.72). There was no significant difference between atypical and typical antipsychotics in risk of sudden cardiac death (IRR 1.14, 95% CI 0.93 to 1.39). Former users of antipsychotics and non-users did not differ significantly in risk of sudden cardiac death (IRR 1.13, 95% CI 0.98 to 1.30). Current users of antipsychotics had a higher risk of sudden cardiac death than former users ($p < 0.001$). There was a dose–response relationship, with higher doses of typical or atypical antipsychotics increasing the risk of sudden cardiac death compared with non-users ($p < 0.001$ for typical, $p = 0.01$ for atypical antipsychotics). Similar results were found if the propensity matched subcohort was used.

CONCLUSIONS

Compared with antipsychotic non-users, current users of typical or atypical antipsychotics have a similarly increased risk of sudden cardiac death.

ABSTRACTED FROM

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Numerous psychotropic drugs have been associated with cardiac conduction changes and this is particularly the case with antipsychotics.¹ Most antipsychotics are associated with prolongation of the QT interval and some have been linked to Torsade de Pointes. A handful of studies have previously linked antipsychotic use to sudden cardiac death but these studies mainly involved the use of older typical antipsychotics.

Ray and colleagues robustly demonstrate that both typical and atypical antipsychotics are associated with a significantly increased rate of sudden cardiac death and that the risk is dose related. This

latter finding substantially strengthens one's confidence in the robustness of the former. The overall rate of sudden cardiac death was extremely low (17.9 deaths per 10 000 patient years) but the 2–3-fold increased risk afforded by the use of antipsychotics is clearly clinically significant.

The present study shows that all antipsychotics are likely to increase the risk of sudden cardiac death regardless of their individual propensity to affect the QT interval. It also provides the most robust evidence to date to support the use of lowest possible doses of all antipsychotics in the treatment of psychosis. No longer should clinicians unthinkingly prescribe higher and

higher doses of antipsychotics, even within licensed dose ranges, assuming such doses to be safe. The clear dose related risk of sudden cardiac death should provoke a marked change in prescribing practice.

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1. **Taylor DM.** Antipsychotics and QT prolongation. *Acta Psychiatr Scand* 2003;**107**:85–95.